REPORT OF STUDY OF ADMINISTRATION OF CONVALESCENT SERUM IN THE TREATMENT OF POLIOMYELITIS

Since Professor Netter of Paris first introduced the therapeutic use of convalescent human poliomyelitis serum in 1911, the therapeutic employment of the serum has gradually extended until it has become widely resorted to wherever convalescent serum can be obtained. In the early years there was little discrimination in its use, paralytic and preparalytic cases being treated indifferently. During the latter period, the tendency has been more and more to restrict the serum to early, preferably preparalytic, cases of the disease. The consensus of opinion has been that the convalescent serum is therapeutically valuable. It has, however, been recognized that epidemic poliomyelitis is clinically a highly variable disease. The manifestations are protean in their variety and degree of severity. As the diagnosis has been increasingly perfected, larger and larger numbers of cases of mild illness have been included in the classification of the malady.

At the time this study was begun no considerable outbreak of poliomyelitis had occurred in New York City since the overwhelming epidemic of 1916. However, indications were not wanting in other parts of the United States, as well as in Europe, that the epidemic disease was again becoming active. In 1926, Dr. George Draper stated that the only hopeful method of treatment of poliomyelitis was by use of convalescent human serum administered in the preparalytic stage of the disease, and he suggested that the Academy of Medicine keep a supply of the serum on hand.

Impressed with the growing severity of outbreaks of poliomyelitis in the United States, Dr. Simon Flexner made a similar suggestion to the Academy, which suggestion was referred to the Public Health Relations Committee in 1928. Before the matter was discussed with the Public Health Relations Committee, the Director conferred

with Dr. Louis I. Harris, then Commissioner of Health, who stated that he had no faciluties for collecting the serum. He approved the proposal that the Academy undertake to collect serum and to distribute it under conditions of control (having in mind a critical study of the therapeutic results obtained).

The Public Health Relations Committee also approved of the project and appointed a special committee consisting of the following:

Dr. Harold L. Amoss	Dr. George Draper	Dr. Josephine B. Neal
Dr. W. Lloyd Aycock	Dr. Simon Flexner	Dr. William H. Park
Dr. E. H. L. Corwin	Dr. Royal S. Haynes	Dr. Philip Van Ingen

Dr. Linsly R. Williams, Chairman

Dr. Philip Van Ingen was appointed Chairman, but was succeeded in the summer of 1928 by Dr. Linsly R. Williams. Miss Gladys Adams served as Secretary during the summer of 1928.

During the earlier meetings of the Committee in the spring of 1928 the following points were considered:

1. The value of convalescent serum and its method of administration
2. The collection of serum
3. Preparation of the serum
4. The administration of the serum and the compilation of records
5. Announcements to the medical profession

Dr. Alfred E. Fischer, a practicing physician in this city, and Dr. Herbert Scheffer, on the staff of Dr. William H. Park at the Health Department Laboratories, cooperated in securing blood from convalescent patients during the first six months. A considerable amount of blood was obtained from the following hospitals: Ruptured and Crippled, New York Orthopedic, Hebrew Home for Crippled Children and the New York State Hospital for Crippled Children. The Committee is very appreciative of the cooperation of the staff of these hospitals.

The amount of blood obtained from these sources was not constant and advertisements were inserted in the papers, asking convalescent patients to appear at a certain time so that blood might be taken from them, and with the cooperation of the Cornell Clinic, patients were seen there

on Saturday afternoons. A considerable amount of blood was obtained in this manner. The blood was taken to the laboratory of the City Department of Health, where the serum was prepared and several doses were distributed to the cooperating physicians. (For method of preparation see Appendix A.) This procedure was carried out in the summers of 1928, 1929, 1930 and 1931. During the first three summers a sufficient amount of serum was available as a very limited number of cases occurred in the city. In the summer of 1931, with a far larger number of cases, it was impossible to secure a sufficient amount of convalescent blood serum.

No definite rate of payment was determined upon to convalescent blood donors. A number of individuals who were well to do offered their blood gratuitously but in general most of the donors were paid from $5 to $10 and in many instances carfare or taxi fare was paid.

Administration of Serum

It was clear from the outset that the object of the Committee was to make a clinical study and not to supply every demand. Physicians were appointed by the committee and paid for rendering the following service:

1. Consultation with the family physician
2. Making complete examination and recording it on proper forms
3. Performing a spinal puncture
4. Making a cell count at the bedside
5. Administering the serum intraspinally and intramuscularly or intraspinally and intravenously
6. Making a second visit to administer second dose of serum on second day
7. Making subsequent follow-up visit

The physicians selected were chosen on account of their hospital experience and technical training and the fact that they would be available throughout the summer for work at any time.

After several discussions the Committee approved of a series of regulations which were distributed to the cooperating physicians. (See Appendix B.) It was also agreed by the Committee that a family would be asked to pay $25

for the consultation, examination and administration of the serum to repay in part the cost of the collection and preparation of the serum and for payments to the physicians. It was suggested that in some instances families might be willing to contribute more than that sum, but that no money was to be demanded of families who could not afford to pay. The following physicians acted as cooperating physicians during the summer of 1928, 1929, 1930 and 1931:

1928	Harry Mackler	Harry Mackler
H. W. Dargeon	James R. Reuling	William Messer
Leonard T. Davidson	Stanley Pettit	
Alfred E. Fischer	E. D. Scala	1931
T. T. Mackie		Alfred E. Fischer
Carl Smith	1929	Jacques Lewis
Scott Johnson	Alfred E. Fischer	Sidney Leader
Herbert Scheffer	Jacques Lewis	Harry Mackler
Charles Weymuller	Harry Mackler	Carl Smith
Lambert Krahulik	William Messer	William Messer
Joseph C. Regan	Joseph C. Regan	Stanley S. Lamm
Samuel Cohen		David Merksamer
William Messer	1930	K. Kingsley
David Greene	Alfred E. Fischer	Milton E. Robbins
Herman Frosch	Jacques Lewis	Harry S. Lichtman

The Committee also discussed at one of its meetings the possibility that physicians might oppose this type of work and that the family physician might object to having the serum administered by the cooperating physician. It was found in a number of cases that the family physician desired to administer the serum himself, though in most instances he preferred to have the serum administered by one of the cooperating physicians. No difficulties were experienced with physicians in this regard during the first three summers. During the summer of 1931 several complaints were made by physicians. Upon investigation these were found to be unreasonable.

Announcements to Physicians

Experience with earlier epidemics had indicated that there were many physicians who had never seen a case of poliomyelitis in the early stages. It was felt that treatment with convalescent serum was only of value in early

cases in the preparalytic stage. The following procedure was carried out: with the cooperation of the Commissioner of Health of the City, articles were published each year in the Bulletin of the City Department of Health, on the early diagnosis of poliomyelitis. These were prepared by Dr. George Draper. Announcements were also made in the Bulletin giving the names, addresses and telephone numbers of the physicians engaged in the study.

Medical Week, a weekly bulletin of medical announcements and medical news, published by the Medical Society of the County of New York, also rendered cooperation by carrying each year brief statements of the object of the study, the methods to be employed, the charges to be made, and the names, addresses and telephone numbers of the physicians.

Statements or interviews were not issued to the press as it was felt that it would be wiser if patients were referred by their family physicians and did not come directly to the physicians engaged in the study. There were, however, several interviews given to representatives of the press in the spring and summer of 1928, at the time that advertisements were inserted in the press to reach convalescent poliomyelitis cases who would be willing to serve as blood donors, as this was a novel procedure.

Experience of 1928, 1929 *and* 1930

In 1928, 521 cases of poliomyelitis were reported to the Health Department of the City of New York during the five months, June to October inclusive. There were 125 deaths, a case fatality rate of 26%. Sixty-one of these cases were treated with serum, among which there were 18 deaths, a case fatality rate of 29%. Twenty-one of these cases were treated in the preparalytic stage and there were 3 deaths, a case fatality rate of 14%. An effort was made to compare these cases with the number treated in the city hospitals of which there were 767, without any satisfactory conclusion.

During the four summer months of 1929 there were 38 cases of poliomyelitis reported in the city. Serum was

administered to 6 cases, 4 of which were treated in the preparalytic stage, and of these, 3 recovered without paralysis.

In 1930 there were 27 cases reported to the Health Department during the four summer months. Of these 14 were treated, 6 in the preparalytic stage, 5 of which entirely recovered.

Experience of 1931

The number of cases reported to the City Health Department during the year was 4,154, of which 4,058 occurred during the months of June, July, August, September and October. Five hundred and two deaths were reported, a case fatality rate of 12.1%. The Committee's physicians visited approximately 800 cases. During part of this period it was not possible to respond to every call or to administer serum as the amount was at times either limited or not available. Four hundred and seventy-seven cases were treated in the preparalytic stage and among these there were 18 deaths, a case fatality rate of 3.8%. Observations were made of 102 cases in which no serum was administered, and in these cases there were two deaths, a case fatality rate of 2%.

Statistical Study

The completed record cards of 477 cases were submitted to statisticians who compiled tables which show the monthly incidence of cases, the extent of paralysis of the treated and untreated cases at the time of visit and the resulting paralysis of 459 of these cases. The paralyzed cases were classified at the time of discharge and again three months later. The usual tables were also made in regard to sex and age incidence, as well as temperature, onset and cell count. Tables were also compiled indicating the results of treatment by different days from the onset of meningeal symptoms and the result in accordance with the amount of serum administered.

As the serum was administered either intraspinally and intravenously or intraspinally and intramuscularly, these

results were also tabulated. A comparison was also made between the cases selected for treatment with serum and those not treated.

Consideration of the Results of the Poliomyelitis Study

As indicated earlier in this report, it was felt that it would not be possible to state whether the convalescent serum was of real value or not unless a comparison was made between the treated group and the untreated group of patients.

Several considerations immediately arise which color the entire situation:

Among the 4,154 cases reported in the city during the year 1931, the case fatality rate was over 12% and the case fatality rate among the 477 treated cases was 3.6%. This fact, however, does not warrant the conclusion that the treatment produced a far better result in terms of lower mortality. The following questions also suggest themselves: How many unreported mild cases were there in which there were only prodroma or mild meningeal symptoms not developing paralysis? How many other forms of mild cases with slight weakness or temporary paralysis were not reported? Were the cases referred to the physicians cooperating in the study in general of a milder nature than those reported to the Health Department? Did the family physicians who sought the serum treatment for their patients recognize the fact that it was useless to treat bulbar or frankly paralyzed cases? Was this group of physicians better informed on the diagnosis of poliomyelitis and did they seek the serum treatment as soon as they suspected poliomyelitis? Naturally, these questions cannot be answered any more than if one were making a similar study in a similar way of the results of treatment in any other disease.

When one goes farther, as was done during the period in which no serum was available when 102 untreated cases were followed and it was found that in this group the mortality was slightly less than 2%, a similar series of

questions arises. First, were the treated and the untreated group comparable? In an endeavor to ascertain whether or not the untreated group was a milder group than the treated group, each physician was asked to classify his cases as "mild," "fairly ill," "seriously ill," or "extremely ill." Statistical analysis of the data based on this grading of the cases comparing the treated with the untreated group and computing the difference between the two groups with relation to the seriousness of the illness of the individual cases composing them, show that the untreated group was indeed a much milder group than the treated group. There were also differences in age distribution and other factors which may have influenced the end results.

Conclusion

The results of the study are therefore inconclusive. Many of the members of the Committee and the physicians who took part in this study feel that more accurate and more intensive work should be done along these lines.

The Committee expresses its gratitude to the several individuals who contributed funds for the purpose of making this study and also expresses its appreciation of the willingness on the part of many persons previously affected with poliomyelitis, who voluntarily gave of their blood to the Committee. The Committee also expresses its satisfaction with the work performed by the cooperating physicians, who devoted their best efforts under many trying circumstances, not only to help children who were affected with poliomyelitis, but who also kept careful records of the work performed.

LINSLY R. WILLIAMS, *Chairman.*

APPENDIX A

PREPARATION OF POLIOMYELITIS CONVALESCENT SERUM

In selecting convalescent donors for the preparation of serum account is taken of their general physical condition,

age and body weight. The amount of blood taken is determined by these factors. From healthy children 13 to 16, the amount drawn varies between 175 and 250c.c. From adults 500c.c. may be taken if necessary, and in the case of professional donors this amount may be removed once in 3 weeks if their condition allows. It is customary to pay the professional donors $10.00 for 100c.c. drawn. Probably the more recent the attack of poliomyelitis, the more efficient will be the serum, though there is no definite opinion on this. There is evidence of the presence of immune bodies in serum from patients 20 years after the attack.

In drawing the blood, the subject reclines with head slightly elevated. After painting the antecubital region with iodine and washing with alcohol, a tourniquet is applied above the elbow and a large gauge Luer needle is inserted into one of the superficial or deep veins. The needle is connected by sterile rubber tubing to a rubber stoppered sterile 500c.c. wide mouth bottle. The air in the bottle is gently evacuated by means of a small hand suction pump connected by another piece of rubber tubing. The bottle should not be filled over half full of blood so that clotting may take place in a slanting position. After allowing the bottle to stand slantwise, at room temperature for ½ hour it is transferred to a refrigerator and allowed to remain for 24 hours. The more or less clear serum is drawn off in a suitable sterile bottle and the clot is separated from the sides of the bottle with a sterile glass rod, and returned to the refrigerator in an upright position. Within a few hours, additional serum may be poured off. This second lot will contain a great many red cells. Both lots are centrifuged to remove suspended red cells and then pooled. The preservative is then added as follows:

A mixture of tricresol one part, and ether two parts, is freshly prepared and added to the serum in such proportion that the serum will contain 0.3% tricresol. The addition is followed by agitation to thoroughly incorporate

the preservative in the serum. The serum is then passed through a mat of pulped filter paper and then through a Berkefeld Filter, W grade, and put in ampules, 18c.c. to the ampule. One ampule in every five is first rinsed out with about ¼c.c. of serum, the rinsings being inoculated into a tube of deep veal broth. This serves as a sterility test for the serum, ampule and technique.

If it is not possible to obtain a recent Wassermann report on any donors used, a Wassermann test may be performed on the pooled serum from several individuals.

APPENDIX B

COMMITTEE ON POLIOMYELITIS

Instructions For Physicians Cooperating With The Poliomyelitis Comm.

1. The Committee on the study of the therapeutic value of convalescent serum for poliomyelitis has a limited sum of money available for trying out the value of the serum.
2. It is known that the cost of obtaining the serum alone will be approximately $40 per treatment.
3. It is hoped that a proportion of this sum will be repaid by those receiving the treatment.
4. A sufficient amount of serum to treat two cases will be sent to each one of the cooperating physicians from the research laboratory of the Department of Health as soon as it is available. These doses will be accompanied by sterile flasks for spinal fluid.
5. The serum must be kept in an icebox until used.
6. Family physicians will usually call upon the cooperating physician from the Borough in which the cooperating physician lives and he will be expected to respond to any call.
7. When a cooperating physician receives a call from a

physician he will explain to him that the family will be expected to pay $25 for the serum, which is less than the cost of obtaining it, and that there will be no charge for its administration.

8. The cooperating physician will also advise the physician to give the patient a dose of magnesium sulphate of such amount as the family physician deems necessary in accordance with the size of the patient.

9. A diagnosis will be difficult unless in the presence of a real epidemic, but if a probable diagnosis is made by making a cell count of the spinal fluid, the remaining spinal fluid withdrawn is to be placed in the sterile flask provided for the purpose and sent by hand to the Department of Health Laboratory, Foot of East 16th Street, in care of Dr. Neal, where further examination will be made.

10. The cooperating physician will then give the serum by one of the following methods, viz:
    a. 20c.c. intraspinally and 50c.c. intravenously or intramuscularly.
    b. 70c.c. intravenously or intramuscularly or both, depending on the condition of the patient.

11. Approximately twenty-four hours thereafter a second dose of 20c.c. will be given intraspinally if the first dose was given in this manner. If the first dose was given intravenously or intramuscularly, the second dose of 20c.c. should be given by the same route as the first dose.

12. Some people object strenuously to the administration of serum. In such cases the explanation should be made that the serum comes from human beings who are normal except that they have had poliomyelitis, and that their blood has been tested to be sure that it is free from any impurities.

13. A supplementary visit by the same cooperating physician will be made from two to three weeks after the

administration of the serum to ascertain the result, unless this can be learned satisfactorily from the family physician.

14. It is believed that the serum is of value in the preparalytic stage of the disease and it should not be given if paralysis has existed for over twelve hours. It must be remembered that the serum is presumably of no value after the paralysis has been recognized and that the amount of serum available for use will be very limited.

15. The report cards will be filled out at the bedside and mailed to the Poliomyelitis Committee, The New York Academy of Medicine, 2 East 103rd Street; a check for $25 should accompany the record. In the case of known indigent families, payment will not be possible and an explanation of this fact should accompany the report.

16 Upon receipt of the report card which indicates that serum has been administered, the Academy will notify the Health Department Laboratory, and see that an additional dose of the serum is mailed to the physician.

17. The cooperating physician will be paid by the Academy committee $10 for the first visit and $5 for the second and third visits, a total of not over $15 per patient treated.

18. It would be well if the cooperating physicians carried a copy of these instructions with them to show to the family physician or the family if necessary.